A Company of the Fresenius Kabi Group

April 8, 2011

Product Name/Product size	Lot Number	Product Code	NDC Number
Cytarabine Injection 2g/ 20mL (100mg/ mL), 20mL Single Dose Vial	**6101775**	**102020**	**63323-120-20**

Dear Healthcare Provider:

On February 11, 2011, APP Pharmaceuticals, LLC, (APP) a company of the Fresenius Kabi Group voluntarily initiated a recall of Cytarabine Injection 2g/ 20mL (100mg/ mL), 20mL Single Dose Vial, Product Code 102020, Lot 6101204 to the retail level. APP decided to take this action due to customer complaints regarding particulate in the vial that has been identified as precipitated crystals of the cytarabine product. The preliminary review of the manufacturing data at the time of the recall did not reveal any deviations or incidents that would have contributed to the crystallization of the product. However, as product with known visible particulate should not be used, and as a precautionary measure, due to this atypical trend in customer complaints for this single lot, APP recalled this lot of Cytarabine Injection 2g/ 20mL (100mg/ mL) lot 6101204.

To date, the most probable root cause for the formation of crystals in the Cytarabine Injection Single Dose vial has been determined to be intermittent filling of the finished product solution. Additionally, based on preliminary studies, evidence has shown that storage conditions below the room temperature conditions listed within the product literature, stating to store at 20° to 25° C (68° to 77° F), can facilitate the formation of crystals.

The crystal formation phenomenon, at this rate, has not been demonstrated by any other lot of APP Cytarabine Injection 2g/ 20mL (100mg/ mL), 20mL Single Dose Vial even when exposed to temperatures below room temperature as noted earlier. This data, along with a detailed review of APP's manufacturing process and customer complaint history for this product and this defect, confirm that there is no evidence that would suggest other lots of Cytarabine Injection have been impacted by this event other than the recalled lot, Cytarabine Injection 2g/ 20mL (100mg/ mL), 20mL Single Dose Vial, Lot 6101204.

APP has been made aware that there is a severe shortage of Cytarabine. To assist in alleviating a continued shortage of this important chemotherapeutic drug and with the agreement of the Food and Drug Administration, APP has re-inspected undistributed product from the recalled lot for visible crystals. Product vials not containing the visible crystals have been relabeled with a new lot number for market distribution. The new product identifier is Cytarabine Injection 2g/ 20mL (100mg/ mL), 20mL Single Dose Vial, Lot 6101775. Each individual carton of Cytarabine Code 102020 will contain 1 copy of this Dear Healthcare Professional letter.

As stated in the package insert, Cytarabine Injection vials should be stored at room temperature 20º to 25ºC (68º to 77ºF). Excursions permitted to 15º to 30ºC (59º to 86ºF). The vial should be protected from light and retained in the carton until the contents are used. **Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If a precipitate or crystals occur, resolubilize immediately before use by heating to 40°C (104°F), for not more than 120 minutes and shaking vigorously; allow to cool to body temperature before using.**

Injectable products containing precipitate or crystals should not be used. Please review the complete prescribing information before administering Cytarabine Injection.

APP has begun new manufacturing of Cytarabine with additional monitoring to prevent the intermittent filling of the finished product solution. Additional testing and subsequent product inspection will be done as well for purposes of detecting the presence of crystals.

APP Pharmaceuticals has NOT received reports of any adverse events that would be attributable to particulate matter in patients receiving Cytarabine Injection. The administration of crystals, precipitate or

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other particulates if present in a parenteral drug poses a potential safety risk to patients. Though there is relatively little data in the literature regarding inadvertent administration of particulate matter in injectable pharmaceuticals, isolated case reports suggest that sequelae of thromboembolism, some life-threatening (such as pulmonary emboli), may occur. There have also been reports of particulate possibly causing phlebitis, mechanical block of the capillaries or arterioles, activation of platelets, subsequent generation of microthrombi, and emboli. Administration of a crystal or particulate can also lead to formation of granulomas, which represent a protective local inflammatory response to the foreign material and are typically non-serious.

There is no specific data on the risk associated with the administration of Cytarabine crystals. It can be postulated that the formation of crystals could result in an unknown drug concentration with the potential for inaccurate dosing. However, based on APP's data all product exhibiting crystals have had assays within stability limits.

The administration of crystals if present in Cytarabine, or the injection of any particulate, therefore represents a potentially significant safety risk. Based on this information and evaluation of the potential health hazard, injectable products containing precipitate or crystals should not be used.

Adverse reactions or quality problems experienced with the use of this product may be reported to the FDA's MedWatch Adverse Event Reporting program either online, by regular mail or by fax.

- **Online**: www.fda.gov/medwatch/report.htm[1]
- **Regular Mail**: use postage-paid FDA form 3500 available at: www.fda.gov/MedWatch/getforms.htm[2]. Mail to MedWatch 5600 Fishers Lane, Rockville, MD 20852-9787
- **Fax**: 1-800-FDA-0178

APP CONTACT NUMBERS: Please use the following contact numbers as appropriate:

Number	Department	Reason to Call
866-716-2459	Quality Assurance Department	Information on DHCP Letter
800-551-7176	Medical Affairs Department	Clinical/Technical Information

We apologize for the inconvenience that you may experience and we appreciate your prompt cooperation. The Food and Drug Administration has been involved in this notification.

Sincerely,

J Frank Harmon

Frank Harmon
Executive Vice President and COO